The role of rubella in the etiology of supravalvular aortic stenosis

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Summary: The possibility of an etiological relationship between rubella embryopathy and sporadic forms of supravalvular aortic stenosis is considered. A case is presented of a patient with rubella embryopathy and supravalvular aortic stenosis associated with pulmonary valvular and peripheral pulmonary artery stenosis, bicuspid aortic valve, aortic valve stenosis and subendothelial myocardial fibrosis. A review of the literature revealed many clinical and pathological features common to both syndromes. The hypothesis that rubella virus produced germ-cell mutation and subsequent persistence of rubella in the zygote produced further fetal damage is presented to explain these observations.

Williams, Barratt-Boyes and Lowe[1] were the first to describe the association of supravalvular aortic stenosis, mental deficiency and peculiar facies. On the other hand, supravalvular aortic stenosis may be associated with normal facies and intelligence and may occur in sporadic or familial forms.[2-8]

There is an overlapping of the clinical features of some patients in these two groups. Patients with supravalvular aortic stenosis may have normal intelligence and characteristic facial and somatic features of the syndrome.[9] Furthermore, such patients may have several siblings similarly affected.[10]

Beuren *et al.*[11] observed multiple peripheral pulmonary artery stenoses in their patients. These lesions were subsequently described in the familial form of supravalvular aortic stenosis associated with normal intelligence and normal appearance.[12] Peripheral pulmonary artery stenosis is therefore a feature in common of the two major but overlapping groups of patients with supravalvular aortic stenosis.

Garcia *et al.*[13] observed the association of infantile hypercalcemia and the supravalvular aortic stenosis syndrome. This is not present in all cases and the relationship has not been established as causal.

Varghese, Izukawa and Rowe[14] reported a patient with rubella embryopathy, patent ductus arteriosus, peripheral pulmonary artery stenosis and supravalvular aortic stenosis. The present report describes a patient with rubella embryopathy syndrome and supravalvular aortic stenosis associated with pulmonary valvular and peripheral pulmonary artery stenosis, bicuspid aortic valve, aortic valvular stenosis and subendothelial myocardial fibrosis (Fig. 1).

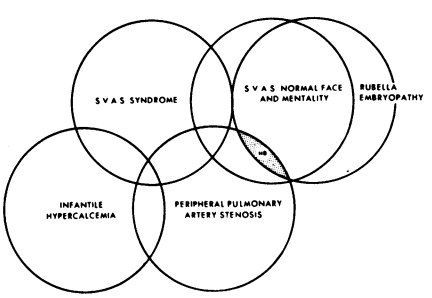

FIG. 1—Diagram illustrating the relationship of supravalvular aortic stenosis (S.V.A.S.) syndrome, peripheral pulmonary artery stenosis, infantile hypercalcemia, rubella embryopathy and familial supravalvular aortic stenosis to the patient H.B.

Case report

This infant girl was the first child of normal, healthy young parents. The father's brother had tetralogy of Fallot. The mother developed the typical rash and illness of rubella four days before her last normal menstrual period. The child was born at term. The birth weight was 2400 g. A cardiac murmur, bilateral microphthalmos and congenital cataracts were observed in the neonatal period. The infant failed to thrive and was given digoxin.

At 8 months of age the child weighed 6050 g. (25th percentile*). The facial appearance was normal

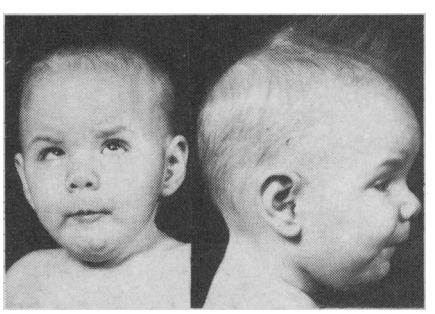

FIG. 2—Patient H.B., aged 8 months. The facial appearance is normal apart from bilateral microphthalmos and cataracts.

*The Children's Medical Center, Boston. Anthropometric chart.

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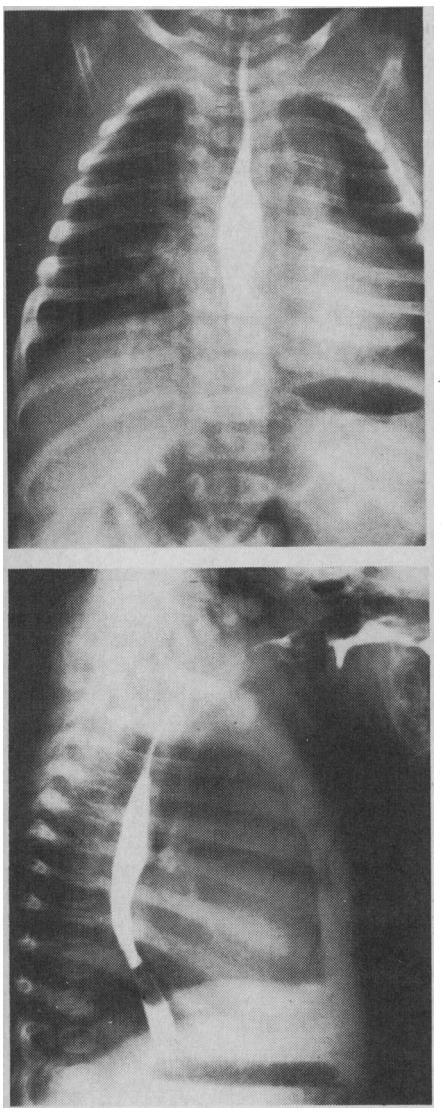

FIG. 3—Chest roentgenogram of H.B. at 8 months of age. (a) Anteroposterior and (b) lateral views with barium swallow.

apart from bilateral microphthalmos and cataracts (Fig. 2). The eye le-

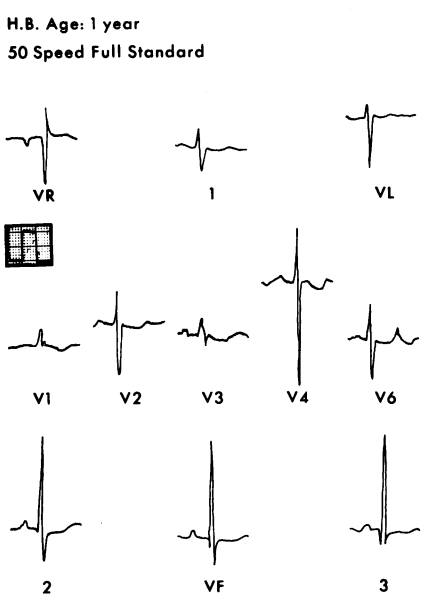

FIG. 4—Electrocardiogram of H.B. at 1 year of age (50 speed, full standard). For interpretation see text.

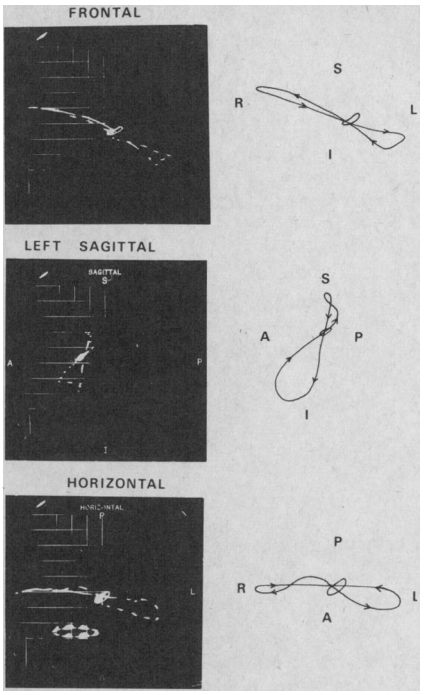

FIG. 5—Frank vectorcardiogram of H.B. at 8 months of age. For interpretation see text.

sions were characteristic of those found in rubella embryopathy syndrome. There was no cyanosis; a systolic thrill was palpable over the precordium and there was a heaving apex beat; the pulmonary component of the second heart sound was moderately accentuated, and the two components of the second heart sound were well split in all phases of respiration. The aortic component of the second heart sound was softened. A harsh, delayed ejection systolic murmur was audible at the base. A faint, early diastolic murmur was audible down the left sternal border. The femoral arterial pulses were palpable and the blood pressure was 80 mm. Hg systolic in both arms and the left leg. The liver edge was palpable 2 cm. below the right costal margin in the anterior axillary line.

The chest roentgenogram with barium in the esophagus showed evidence of right ventricular prominence, a left aortic arch and lung vascular markings which were at the upper limit of normal (Fig. 3). The electrocardiogram demonstrated a combined right and left ventricular hypertrophy pattern, with S-T segment and T-wave changes (Fig. 4). The Frank lead vectorcardiogram suggested combined right and left ventricular hypertrophy with discordant T-wave loops (Fig. 5).

The urinalysis was normal, hemoglobin 12.3 g., serum calcium 10.5 mg., and serum phosphate 4.3 mg. per 100 ml. Rubella antibodies (H.I.) at age 8 months: in the patient 1:512, in the mother 1:2048. Viral cultures of lens material from the right eye and stool showed no growth.

Chromosome studies were not done. Dermatoglyphic patterns of the patient's hands showed bilateral distal displaced axial triradii, bilateral ulnar loops in hypothenar areas of the palms and a simian crease in the left palm.

Cardiac catheterization studies performed at 8 months of age demonstrated pulmonary valvular stenosis and stenosis of the right and left pulmonary arteries distal to the bifurcation associated with post-stenotic dilatation (Fig. 6). In addition there was a bicuspid aortic valve and aortic valvular and supravalvular stenosis (Fig. 7). The withdrawal tracings from left ventricle to ascending aorta demonstrated significant hemodynamic gradients at both valvular and supravalvular levels (Fig. 8).

The patient died rather suddenly after a brief illness at 22 months of age. Necropsy confirmed the cardiovascular diagnosis and, in addition, demonstrated evidence of chronic pulmonary congestion and histological changes in the myocardium, par-

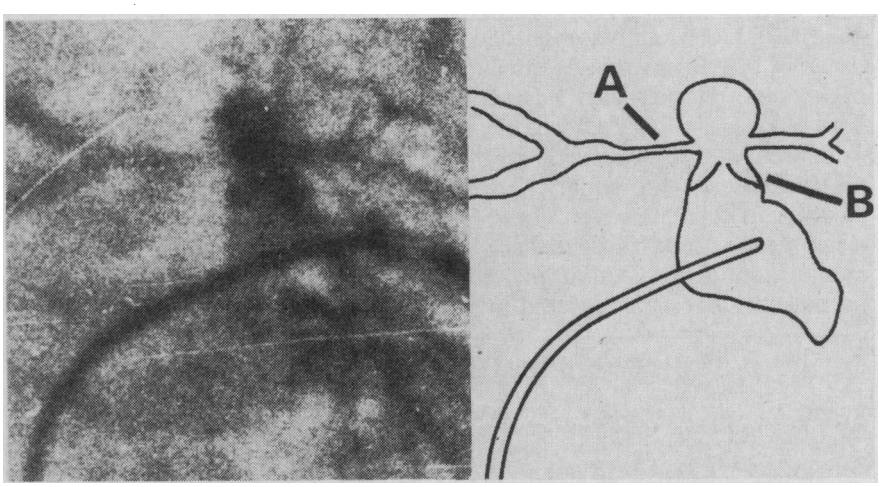

FIG. 6—Single frame cine angiocardiogram anteroposterior view demonstrating (a) stenosis of the pulmonary arteries and (b) pulmonary valvular stenosis.

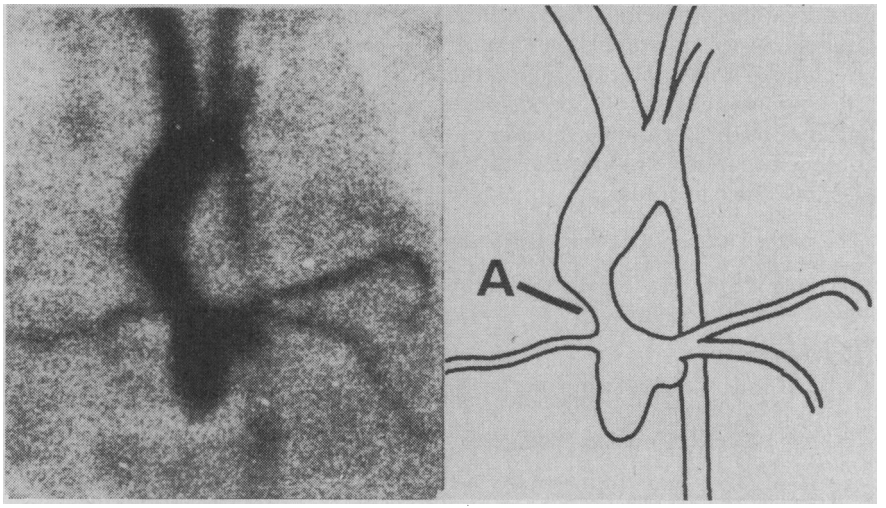

FIG. 7—Single frame cine angiocardiogram anteroposterior view demonstrating aortic valve stenosis, bicuspid aortic valve and supravalvular aortic stenosis (A).

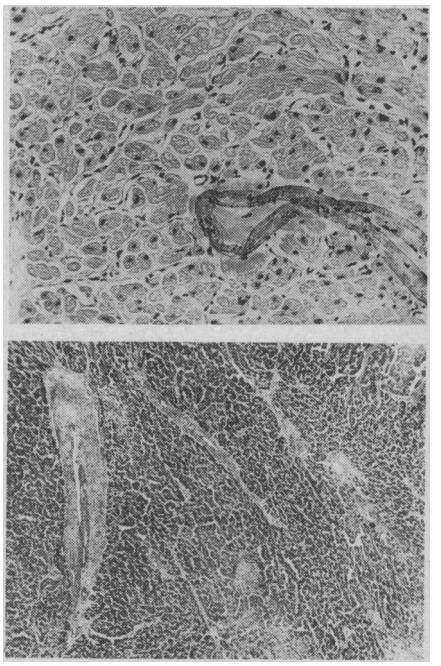

FIG. 10—(a) High power and (b) low power photomicrographs, Masson's trichrome stain. Inner third of left ventricular myocardium demonstrating extensive fibrosis.

ticularly in the left ventricular myocardium. Marked thickening of the endothelium with histological evidence of recent and healed lamellar subendocardial myocardial infarctions was demonstrated (Fig. 9). This myocardial damage was not present in the subpericardial layers of myocardium. Fibrosis was concentrated in the inner one-third of the myocardium (Fig. 10).

Discussion

This patient demonstrated the clinical and pathological features of rubella embryopathy and of supravalvular aortic stenosis. Subendocardial fibrosis and endothelial thickening have not been observed previously in association with either rubella embryopathy or supravalvular aortic stenosis. In the presence of moderate aortic valvular and supravalvular stenosis the degree of fibrosis is rather severe and raises the possibility of there being an additional, unidentified contributing factor.

A review of the literature discloses a remarkable overlapping of the clinical and cardiovascular findings in the cases with supravalvular aortic stenosis and rubella embryopathy. The low birth weight for gestational age and failure to thrive, so commonly observed in infants with rubella embryopathy, have also been described in supravalvular aortic stenosis.[11, 15-17] Peripheral pulmonary artery stenoses are frequently observed in both groups.[11, 12, 18, 19] Myocardial fibrosis has been observed in several patients with supravalvular aortic stenosis,[3, 20] and myocardial damage from viral myocarditis in rubella syndrome has also been documented.[21, 22] Multiple segmental arterial vascular lesions affecting the aorta, renal arteries and coronary arteries are known to occur with rubella embryopathy syndrome.[23] Similar lesions also occur in association with supravalvular aortic stenosis.[17, 24, 25] Moreover, there is a remarkable histological similarity in the arterial lesions.[14, 26] Associated congenital heart malformations such as patent ductus arteriosus,[27] coarctation of the aorta,[27] ventricular septal defect,[5, 27] aortic stenosis,[27, 29] pulmonary valve stenosis[24] and mitral valve thickening[30, 31] have been observed in association with both rubella embryopathy and supravalvular aortic stenosis.[30, 32]

It is possible that the patient we observed developed both supravalvular aortic stenosis and rubella embryopathy as a matter of chance. However, the overlapping of the clinical and pathological findings in these two syndromes as described in the literature suggests that there may be a causal relationship between the two, common to both syndromes.

Another explanation is that rubella alone produced all the lesions. If this were the case, then rubella must be capable of producing all the lesions evident in the familial form of supravalvular aortic stenosis, and this would be rather difficult to accept.

It is generally accepted that the familial form of supravalvular aortic stenosis is the result of genetic abnormalities showing an autosomal dominant mode of inheritance with reduced penetrance and variable manifestations.[33] On the other hand, the etiology of sporadic cases is unknown. It is possible that a germ cell mutation could result in a chromosomal aberration and an individual with the phenotype of the familial

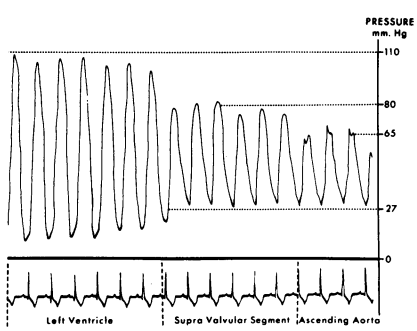

FIG. 8 — Withdrawal pressure tracing from left ventricle to ascending aorta demonstrating hemodynamic gradients at aortic valvular and supravalvular levels.

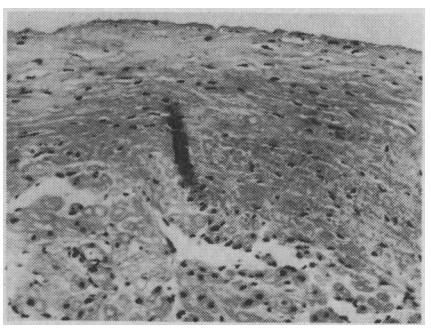

FIG. 9 — Photomicrograph (H. and E. stain) of left ventricular myocardium demonstrating thickening of the endothelium and lamellar subendocardial myocardial infarctions both recent and healed.

form of supravascular aortic stenosis.

This hypothesis is attractive in accounting for our case, since the mother contracted rubella before conception and rubella is known to be capable of producing chromosomal defects.[34, 35] Furthermore, the abnormal dermatoglyphic findings suggest a disturbance in genetic control.[28]

If we do postulate that rubella produced a germ cell mutation and that genetic factors were subsequently responsible for the development of the supravalvular aortic stenosis, then we must also postulate that rubella virus persisted in the zygote and produced the other manifestations of rubella embryopathy demonstrated in our patient. This hypothesis would be supported if it could be shown that during rubella epidemics there was an increased incidence of children born with supravalvular aortic stenosis. If this hypothesis can be proved, the search for viruses which are capable of producing human malformations must be conducted in both parents and cover the interval before conception.

Résumé

Le rôle étiologique éventuel de la rubéole dans la sténose aortique supravalvulaire

L'auteur envisage la possibilité d'une relation étiologique entre une embryopathie rubéoleuse et les formes sporadiques de la sténose aortique supravalvulaire. Il présente le cas d'un malade démontrant cette dualité pathologique accompagnée de sténose de la valvule pulmonaire et de l'artère pulmonaire périphérique, de la valvule aortique bicuspide, de sténose de la valvule aortique et de fibrose subendothéliale du myocarde. Une revue de la littérature pertinente a permis de mettre en évidence que plusieurs de ces caractéristiques cliniques et pathologiques sont communes aux deux syndromes. Pour tenter d'expliquer ces observations, il émet l'hypothèse que le virus rubéoleux peut avoir déclenché une mutation génétique du gamète et que la persistance ultérieure de la rubéole dans le zygote peut avoir provoqué d'autres lésions chez le fétus.

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